

WHAT IS CLAIMED IS:

1. A method for reducing the toxicity of flavopiridol or an analog thereof, comprising administering said flavopiridol, or analog thereof, to an animal in combination with an amount of a second agent effective to reduce excretion of an active flavopiridol species through the bile.

2. The method of claim 1, wherein said second agent increases flavopiridol catabolism.

3. The method of claim 2, wherein said second agent increases glucuronosyltransferase enzyme activity.

4. The method of claim 3, wherein said glucuronyltransferase enzyme is selected from the group including uridine 5'diphosphate glucoronyltansferase (UGT)1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A10, UGT2B4, UGT2B7, UGT2B15 and UGT2B17.

5. The method of claim 3, wherein said second agent is a dithiolethione.

6. The method of claim 3, wherein said second agent is Oltipraz.

7. The method of claim 3, wherein said second agent is an aryloxy-carboxylic acid, an arylcarboxylic acid, a chlorophenoxy-carboxylic acid or a fibric acid.

8. The method of claim 7, wherein said second agent is clofibrate, ciprofibrate, fenofibrate, bezafibrate, gemfibrozol, tiadenol or probucol.

9. The method of claim 3, wherein said second agent is phenobarbital, dilantin, clonazepam, clotrimazole, buthionine sulfoximine (BSO), cyclophosphamide, ifosphamide, a retinoic acid, rifampin or disulfiram (Antabuse).

10. The method of claim 3, wherein said second agent is a corticosteroid.

11. The method of claim 3, wherein said second agent is an oral contraceptive.

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12. The method of claim 1, wherein said second agent decreases biliary transport.

13. The method of claim 12, wherein said second agent decreases the activity of an ABC protein.

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14. The method of claim 13, wherein said ABC protein is a biliary transport protein.

15. The method of claim 14, wherein said biliary transport protein is p-glycoprotein.

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16. The method of claim 14, wherein said biliary transport protein is bile salt export protein.

17. The method of claim 14, wherein said biliary transport protein is MDR3.

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18. The method of claim 14, wherein said ABC protein is a multi-drug resistance-associated protein (MRP).

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19. The method of claim 18, wherein said multi-drug resistance-associated protein is cMOAT.

20. The method of claim 18, wherein said multi-drug resistance-associated protein is MRP1.

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21. The method of claim 18, wherein said multi-drug resistance-associated protein is MRP5.

22. The method of claim 12, wherein said second agent is a cyclosporine, cephalosporin or a staurosporine.

23. The method of claim 22 wherein said second agent is SDZ 280 446, 3'-Keto-cyclosporin D, cefoperazone or staurosporine.

24. The method of claim 22, wherein said second agent is Cyclosporine A, SDZ PSC 833 (valsopodar) or NA-382.

25. The method of claim 12, wherein said second agent is a calcium channel blocker.

26. The method of claim 25, wherein said second agent is a dihydropyridine analogue, verapamil, dex verapamil, tiapamil, nifedipine, diltiazem, nicardipine, nisoldipine, nimodipine or nitrendipine.

27. The method of claim 12, wherein said second agent is a calmodulin antagonist.

28. The method of claim 27, wherein said second agent is trans-flupenthixol, cis-flupenthixol, clorpenthixol, fluphenazine, chlorpromazine, triflupromazine, trifluoperazine, prochlorperazine or thioridazine.

29. The method of claim 12, wherein said second agent is progesterone, a progesterone metabolite, pregnenolone, RU 486 or tirilazad.

30. The method of claim 12, wherein said second agent is reserpine, dipyridamole, chloroquine, propranolol, terfenadine, ivermectin or quinidine.

31. The method of claim 12, wherein said second agent is an antibody that binds one or more biliary transporter proteins.

32. The method of claim 12, wherein said second agent is a cytokine.

33. The method of claim 32, wherein said cytokine is interferon- β .

5 34. The method of claim 12, wherein said second agent is ritonavir

35. The method of claim 12, wherein said second agent is MK571.

36. The method of claim 12, wherein said second agent is genistein.

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37. The method of claim 12, wherein said second agent is a reduced folate.

38. The method of claim 12, wherein said second agent is probenecid.

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39. The method of claim 12, wherein said second agent is a non-steroidal anti-inflammatory drug.

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40. The method of claim 39, wherein said non-steroidal anti-inflammatory drugs is selected from the group including indomethacin, sulindac, tolmetin, acetaminophen, zomepirac, mefenamic acid, ibuprofen, ketoprofen, piroxicam, naproxen, sulindac, aspirin, choline subsalicylate, diflunisal, fenoprofen, meclofenamate, salsalate, tolmetin, etodolac, nabumetone, oxaprozin, rofecoxib, celecoxib, diflunisal, salsalate, ketorolac, tolectin, clinoril, mefenamic acid, fenoprofen calcium, meclofenamate sodium, piroxicam, diclofenac and magnesium salicylate.

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41. The method of claim 1, comprising administering said flavopiridol compound in combination with a second agent that increases conjugative enzyme activity and a third agent that decreases biliary transport protein activity.

42. A method for treating an animal with cancer, comprising administering to said animal a therapeutically effective combination of a flavopiridol drug and a second agent that reduces excretion of the active flavopiridol species through the bile.

43. The method of claim 42 wherein said second agent is administered to the animal prior to said flavopiridol drug.

44. The method of claim 42 wherein said flavopiridol drug or said second agent are administered parenterally.

45. The method of claim 42 wherein said flavopiridol drug or said second agent are administered orally.

46. The method of claim 42 wherein said animal is a human patient.

47. The method of claim 42, wherein said second agent increases the activity of a conjugative enzyme or decreases the activity of a biliary transport protein.

48. The method of claim 42 wherein said second agent increases glucuronosyltransferase enzyme activity.

49. The method of claim 42 wherein said second agent is selected from the group including Oltipraz, clofibrate, ciprofibrate, fenofibrate, bezafibrate, gemfibrozil, tiadenol, probucol, phenobarbital, dilantin, clonazepam, clotrimazole, buthionine sulfoximine (BSO), cyclophosphamide, ifosfamide, a retinoic acid, a corticosteroid, an oral contraceptive, rifampin and disulfiram (Antabuse).

50. The method of claim 42 wherein said second agent is phenobarbital, Oltipraz, all-trans retinoic acid, phenytoin, dexamethasone, rifampin or clofibrate.

51. The method of claim 47 wherein said second agent decreases biliary transport protein activity.

52. The method of claim 51, wherein said second agent is selected from the group including SDZ 280 446, 3'-Keto-cyclosporin D, cefoperazone, staurosporine, Cyclosporine A, SDZ PSC 833 (valspodar), NA-382, dihydropyridine analogue, verapamil, dex verapamil, tiapamil, nifedipine, diltiazem, nicardipine, nisoldipine, nimodipine, nitrendipine, trans-flupenthixol, cis-flupenthixol, clorpenthiol, fluphenazine, chlorpromazine, triflupromazine, trifluoperazine, prochlorperazine, thioridazine, progesterone, a progesterone metabolite, pregnenolone, RU 486, tirilazad, reserpine, dipyridamole, chloroquine, propranolol, terfenadine, ivermectin, quinidine [(3)H]2,4-Dinitrophenyl-S-glutathione (DNP-SG), [(3)H]17beta-estradiol 17-beta-D-glucuronide, dipyridamole (E(2)17betaG), 7-chloro-4-nitrobenz-2-oxa-1,3-diazole, buthionine sulfoximine, MK751, leukotriene C4 (LTC4), bromosulphophthalein (BSP), enalapril, CRC 220, taurocholate (TCA), N-acetylcysteine and cysteine, [3H]Temocaprilat, estradiol-17beta-D-glucuronide, dibromosulphophthalein, genistein, probenecid, ritonavir, indomethacin, sulindac, tolmetin, acetaminophen, zomepirac, mefenamic acid, ibuprofen, ketoprofen, piroxicam, naproxen, sulindac, aspirin, choline subsalicylate, diflunisal, fenoprofen, meclofenamate, salsalate, tolmetin, etodolac, nabumetone, oxaprozin, rofecoxib, celecoxib, diflunisal, salsalate, ketorolac, tolectin, clinoril, mefenamic acid, fenoprofen calcium, meclofenamate sodium, piroxicam, diclofenac magnesium salicylate and interferon α .

53. The method of claim 42, comprising administering a therapeutically effective combination of flavopiridol drug, a second agent that increases conjugative enzyme activity and a third agent that decreases biliary transport protein activity.

54. The method of claim 42, comprising administering about 25-100 mg/m²/day flavopiridol by infusion over about 90 minutes, about 90 mg of phenobarbital and about 5 mg/kg cyclosporine A by infusion.

55. A composition comprising a flavopiridol drug in combination with a second agent that increases conjugative enzyme activity or that decreases biliary transport protein activity.

5 56. The composition of claim 55, wherein said second agent increases glucuronosyltransferase enzyme activity.

10 57. The composition of claim 56, wherein said second agent is selected from the group including Oltipraz, clofibrate, ciprofibrate, fenofibrate, bezafibrate, gemfibrozil, tiadenol, probucol, phenobarbital, dilantin, clonazepam, clotrimazole, buthionine sulfoximine (BSO), cyclophosphamide, ifosphamide, a retinoic acid, a corticosteroid, an oral contraceptive, rifampin and disulfiram (Antabuse).

15 58. The composition of claim 57, wherein said second agent is phenobarbital, Oltipraz, all-trans retinoic acid, phenytoin, dexamethasone, rifampin or clofibrate.

59. The composition of claim 55, wherein said second agent decreases biliary transport protein activity.

20 60. The composition of claim 59, wherein said second agent is selected from the group comprising SDZ 280 446, 3'-Keto-cyclosporin D, cefoperazone, staurosporine, Cyclosporine A, SDZ PSC 833 (valspodar), NA-382, dihydropyridine analogue, verapamil, dex verapamil, tiapamil, nifedipine, diltiazem, nicardipine, nisoldipine, nimodipine, nitrendipine, trans-flupenthixol, cis-flupenthixol, clorpenthiol, 25 fluphenazine, chlorpromazine, triflupromazine, trifluoperazine, prochlorperazine, thioridazine, progesterone, a progesterone metabolite, pregnenolone, RU 486, tirilazad, reserpine, dipyridamole, chloroquine, propranolol, terfenadine, ivermectin, quinidine [(3)H]2,4-Dinitrophenyl-S-glutathione (DNP-SG), [(3)H]17beta-estradiol 17-beta-D-glucuronide, dipyridamole (E(2)17betaG), 7-chloro-4-nitrobenz-2-oxa-1,3-diazole, 30 buthionine sulphoximine, MK751, leukotriene C4 (LTC4), bromosulfophthalein (BSP), enalapril, CRC 220, taurocholate (TCA), N-acetylcysteine and cysteine, [3H]Temocaprilat,

estradiol-17beta-D-glucuronide, dibromosulphophthalein, genistein, probenecid, interferon
α, indomethacin, sulindac, tolmetin, acetaminophen, zomepirac, mefenamic acid, ibuprofen,
ketoprofen, piroxicam, naproxen, sulindac, aspirin, choline subsalicylate, diflunisal,
fenoprofen, meclofenamate, salsalate, tolmetin, etodolac, nabumetone, oxaprozin,
5 rofecoxib, celecoxib, diflunisal, salsalate, ketorolac, tolectin, clinoril, mefenamic acid,
fenoprofen calcium, meclofenamate sodium, piroxicam, diclofenac magnesium
salicylate and ritonavir.

61. The composition of claim 55, dispersed in a pharmacologically acceptable
10 formulation.

62. A therapeutic kit comprising, in suitable container means, a pharmaceutical
formulation of a flavopiridol drug and a pharmaceutical formulation of a second agent
that increases glucuronosyltransferase enzyme activity or that decreases biliary transport
15 protein activity.

63. The kit of claim 62, wherein said flavopiridol drug and said second agent are
present within a single container means.

64. The kit of claim 62, wherein said flavopiridol drug and said second agent are
20 present within distinct container means.

65. The kit of claim 62, wherein said pharmaceutical formulation is suitable for
parenteral or oral administration.

66. The kit of claim 62, wherein said second agent is phenobarbital, Oltipraz, all-trans
retinoic acid, phenytoin, dexamethasone, rifampin or clofibrate.

67. The kit of claim 62, comprising flavopiridol, a pharmaceutical formulation of a
second agent wherein said second agent is selected from the group comprising
30 SDZ 280 446, 3'-Keto-cyclosporin D, cefoperazone, staurosporine, Cyclosporine A,

SDZ PSC 833 (valspodar), NA-382, dihydropyridine analogue, verapamil, dex verapamil, tiapamil, nifedipine, diltiazem, nicardipine, nisoldipine, nimodipine, nitrendipine, trans-flupenthixol, cis-flupenthixol, clorphenoxol, fluphenazine, chlorpromazine, trifluoperazine, prochlorperazine, thioridazine, progesterone, a
 5 progesterone metabolite, pregnenolone, RU 486, tirilazad, reserpine, dipyridamole, chloroquine, propranolol, terfenadine, ivermectin, quinidine [(3)H]2,4-Dinitrophenyl-S-glutathione (DNP-SG), [(3)H]17beta-estradiol 17-beta-D-glucuronide, dipyridamole (E(2)17betaG), 7-chloro-4-nitrobenz-2-oxa-1,3-diazole, buthionine sulphoximine, MK751, leukotriene C4 (LTC4), bromosulphophthalein (BSP), enalapril, CRC 220, taurocholate
 10 (TCA), N-acetylcysteine and cysteine, [3H]Temocaprilat, estradiol-17beta-D-glucuronide, dibromosulphophthalein, genistein, probenecid, interferon α , indomethacin, sulindac, tolmetin, acetaminophen, zomepirac, mefenamic acid, ibuprofen, ketoprofen, piroxicam, naproxen, sulindac, aspirin, choline subsalicylate, diflunisal, fenoprofen, meclofenamate, salsalate, tolmetin, etodolac, nabumetone, oxaprozin, rofecoxib, celecoxib, diflunisal,
 15 salsalate, ketorolac, tolectin, clinoril, mefenamic acid, fenoprofen calcium, meclofenamate sodium, piroxicam, diclofenac magnesium salicylate. and ritonavir.

68. A method for predicting the degree of a flavopiridol drug toxicity in a patient, comprising determining the glucuronidation or biliary transport capacity of the patient,
 20 wherein a decreased glucuronidation capacity or an increased biliary transport capacity, in comparison to normal levels, is indicative of a patient at risk of flavopiridol drug toxicity.

69. The method of claim 68, comprising determining the relevant genotype of the
 25 patient.

70. The method of claim 68, comprising determining the relevant phenotype of the patient.

71. The method of claim 68, comprising determining the glucuronidation capacity of
 30 the patient.

72. The method of claim 68, wherein the glucuronidation capacity of the patient is determined by administering a glucuronidatable substrate to said patient and determining the degree of glucuronidation of said substrate.

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73. The method of claim 72, wherein said substrate of glucuronidation is acetaminophen, diflunisal or morphine.

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74. A method for reducing the toxicity of a flavopiridol compound, comprising administering said flavopiridol compound to an animal in combination with an amount of Cyclosporine A effective to reduce excretion of an active flavopiridol species through the bile by decreasing the activity of a biliary transport protein.

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75. The method of claim 3, wherein said glucuronyltransferase enzyme is a uridine 5'diphosphate glucuronyltransferase (UGT)1A1, UGT1A3, UGT1A4, UGT1A7, or UGT1A9.

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76. The method of claim 75, wherein said glucuronyltransferase enzyme is UGT1A9.

77. A method for evaluating the risk of flavopiridol-induced toxicity in a patient comprising evaluating a UGT1A9-encoding nucleic acid of the patient for a polymorphism.

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78. The method of claim 77, further comprising identifying a patient at risk for flavopiridol-induced toxicity.

79. The method of claim 77, further comprising identifying a polymorphism in a UGT1A9-encoding nucleic acid of the patient.

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80. The method of claim 79, wherein the nucleic acid is encoded by SEQ. ID. NO. 1.

81. The method of claim 79, wherein the nucleic acid is encoded by SEQ. ID. NO. 3.

82. The method of claim 77, wherein the polymorphism results in a decreased level of UGT1A9 activity in the patient.

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83. The method of claim 77, wherein the polymorphism results in a decreased level of UGT1A9 expression in the patient.

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84. The method of claim 77, further comprising identifying a polymorphism in an ABC gene.

85. A method for reducing the toxicity of flavopiridol or an analog thereof in a cancer patient comprising

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a) identifying a polymorphism in a *UGT1A9* gene in a sample from the patient, wherein the polymorphism contributes to reduced expression or activity of the *UGT1A9* gene product; and

b) administering to the patient a second agent effective to reduce excretion of an active flavopiridol species through the bile.

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86. The method of claim 13, wherein the ABC protein is ABCA1, ABCA2, ABCA3, ABCA4, ABCA5, ABCA6, ABCA7, ABCA8, ABCA9, ABCA10, ABCA11, ABCA12, ABCA13, ABCA14, ABCB1, ABCB2, ABCB3, ABCB4, ABCB5, ABCB6, ABCB7, ABCB8, ABCB9, ABCB10, ABCB11, ABCC1, ABCC2, ABCC3, ABCC4, ABCC5, ABCC6, ABCC7, ABCC8, ABCC9, ABCC10, ABCC11, ABCC12, ABCC13, ABCD1, ABCD2, ABCD3, ABCD4, ABCE1, ABCF1, ABCF2, ABCF3, ABCG1, ABCG2, ABCG4, ABCG5, or ABCG8.

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87. The method of claim 86, wherein the ABC protein is BCRP1.

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88. A method for evaluating the risk of flavopiridol-induced toxicity in a patient comprising evaluating a ABC-encoding nucleic acid of the patient for a polymorphism.

89. The method of claim 88, further comprising identifying a patient at risk for flavopiridol-induced toxicity.

90. The method of claim 88, further comprising identifying a polymorphism in a ABC-encoding nucleic acid of the patient.

91. The method of claim 88, wherein the polymorphism results in a decreased level of ABC activity in the patient.

92. The method of claim 88, wherein the polymorphism results in a decreased level of ABC expression in the patient.

93. The method of claim 88, wherein the ABC-encoding nucleic acid encodes ABCA1, ABCA2, ABCA3, ABCA4, ABCA5, ABCA6, ABCA7, ABCA8, ABCA9, ABCA10, ABCA11, ABCA12, ABCA13, ABCA14, ABCB1, ABCB2, ABCB3, ABCB4, ABCB5, ABCB6, ABCB7, ABCB8, ABCB9, ABCB10, ABCB1, ABCC1, ABCC2, ABCC3, ABCC4, ABCC5, ABCC6, ABCC7, ABCC8, ABCC9, ABCC10, ABCC11, ABCC12, ABCC13, ABCD1, ABCD2, ABCD3, ABCD4, ABCE1, ABCF1, ABCF2, ABCF3, ABCG1, ABCG2, ABCG4, ABCG5, or ABCG8.

94. The method of claim 93, wherein the ABC-encoding nucleic acid encodes BCRP1.

95. The method of claim 93, wherein the ABC-encoding nucleic acid encodes MRP1.

96. The method of claim 93, wherein the ABC-encoding nucleic acid encodes MRP2.

97. The method of claim 93, wherein the ABC-encoding nucleic acid encodes PGY1.

98. A method for reducing the toxicity of flavopiridol or an analog thereof in a cancer patient comprising

a) identifying a polymorphism in a *ABC* gene in a sample from the patient, wherein the polymorphism contributes to reduced expression or activity of the *ABC* gene product; and

b) administering to the patient a second agent effective to reduce excretion of an active flavopiridol species through the bile.

99. The method of claim 98, wherein the second agent is a UGT1A9 protein.